

REMARKS

Claims 1, 23-36 and 49 are pending in the subject application. Applicants have herein amended claims 1, 29 and 49 to better clarify that “A is a monomer of TKPPR or a monomer of a TKPPR analogue...” No new matter has been added.

The *Final Office Action* appears to reference an election of invention requirement, and appears to further require Applicants to amend their claims to be limited to the elected invention. Applicants respectfully request clarification of the election and amendment requirement before doing so. Specifically, Applicants have reviewed MPEP Chapter 800 and are unable to locate an election of invention provision to review and understand in conjunction with this requirement. The Examiner is respectfully asked to direct Applicants to the appropriate MPEP provision for review and consideration. It is Applicants’ belief that Applicants have adequately responded to an election of species requirement, and thus that no further amendment to the claims is necessary.

Claims 1, 23-36 and 49 have been rejected under 35 U.S.C. § 112, ¶ 2 based on the term “a TKPPR analogue.” Claims 1, 23-36 and 49 have also been rejected under 35 U.S.C. § 112, ¶ 1 also based on the term “a TKPPR analogue.” Claims 1, 23-36 and 49 have been further rejected under 35 U.S.C. § 103(a) over U.S. Patent 5,789,555 (“Pollak”) in view of U.S. Patent No. 6,252,664 (“Barbera-Guillem”). For the reasons set forth below, Applicants traverse each of these rejections.

As an initial matter, Applicants note that the limitation “a TKPPR analogue” had been recited in the pending claims 1, 23-32, 34-36 and 49 as originally filed and was not added as a result of any subsequent amendment. Thus, the 35 U.S.C § 112, ¶¶ 1 and 2 rejections, which have not been asserted in any office actions prior to the *Final Office Action*, were not

necessitated by any amendment of Applicants' claims. MPEP 706.07(a) As such, Applicants respectfully submit that the finality of the *Final Office Action* is premature, and rather, a non-final Office Action should have been issued to give Applicants an opportunity to respond accordingly to those new grounds for rejection. If appropriate, then Applicants respectfully request reconsideration and withdrawal of the finality of the September 21, 2004 *Final Office Action*, and accordingly also request a refund of the fee required for filing a *Request for Continued Examination*. See MPEP § 706.07(d).

I. Claims 1, 23-36 and 49 Satisfy 35 U.S.C. § 112, ¶ 2

Claims 1, 23-36 and 49 have been rejected under 35 U.S.C. § 112, ¶ 2, as purportedly being indefinite as drawn to a monomer of TKPPR or a TKPPR analogue. Applicants respectfully traverse.

Solely to better define the claimed invention, and not for any reasons related to patentability, Applicants have herein amended independent claims 1, 29 and 49 to clarify that “A is a monomer of TKPPR or a monomer of a TKPPR analogue which specifically binds to NP-1 or cells that express NP-1 with avidity that is equal to or greater than TKPPR.”

As an initial matter, Applicants note that the actual limitation which is recited in claims 1, 23-36 and 49 is not just “a TKPPR analogue” as asserted on p. 3 of the *Final Office Action*, but in fact recites “a TKPPR analogue *which specifically binds to NP-1 or cells that express NP-1 with avidity that is equal to or greater than TKPPR.*” (emphasis added to indicate the omitted limitation language). Therefore, Applicants respectfully submit that this claim limitation, when recited in its entirety, is clear and definite under 35 U.S.C. § 112, ¶ 2.

Additionally, Applicants further submit that the term “analogue” in and of itself is also clear. An “analogue” (or “analog” as it is sometimes spelled) is a well known and well understood chemical term defined as a structural derivative of a parent compound that often differs from it by a single element (*The American Heritage Dictionary of the English Language*, 4th Ed. 2000). One of ordinary skill in the art of chemistry would undoubtedly know and understand what is an “analogue” or “analog.” The USPTO has confirmed this conclusion by issuing over 500 patents in Class 514 (Drug, bio-affecting and body treating compositions) alone which contain the term “analogue” in the claims. The USPTO has also issued over 1,000 patents in this Class 514 alone which contain the term “analog” in the claims. Indeed, a search of “analogue” or “analog” on the USPTO website in all of the possible drug, biological or chemical classes yields thousands of hits for issued U.S. Patents with the term “analogue” or “analog” in the claims. This is compelling evidence that the term “analogue” is clear and definite, and satisfies 35 U.S.C. § 112, ¶ 2.

Furthermore, when such term is clear, definite and understood in the art, there is no requirement that the specification define it as asserted on p. 3 of the *Final Office Action*. In any event, the present Specification states that analogues of TKPPR may include molecules that target the VEGF receptor NP-1 with avidity that is greater than or equal to TKPPR (*see* Specification, p. 10, lines 27-30). The Specification further states that “[o]ne of ordinary skill will appreciate that these analogues may also contain modifications which include substitutions, and/or deletions and/or additions of one or several amino acids, insofar that these modifications do not negatively alter the biological activity of the peptides described herein.” (*See id.* at p. 10, lines 30-33).

To further clarify, and contrary to the statement in the *Final Office Action*, a TKPPR tetramer is not the same thing as a TKPPR analogue. As is well understood in the art by one of ordinary skill, a TKPPR tetramer is a TKPPR multimer containing four (4) TKPPR monomers. On the other hand, a monomer of a TKPPR analogue is a structural derivative of a TKPPR monomer that often differs from TKPPR by a single element, but retains receptor avidity that is greater than or equal to TKPPR. Examples of acceptable TKPPR analogues are listed throughout the Specification, *e.g.*, at pages 10-11. For example, the Specification states that the present invention contemplates TKPPR analogues that result from, *e.g.*, amino acid substitutions, “made with synonymous groups” (page 11, lines 10-15); deletions or insertions of amino acids and muteins or peptides or polypeptides (page 11, lines 24); and peptidomimetics or pseudopeptides incorporating changes to the amide bonds of the peptide backbone (page 11, lines 25-27).

In light of these various statements in the specification and the meaning of the term to the skilled artisan, Applicants respectfully submit that the term “a TKPPR analogue” is clear and definite, and satisfies 35 U.S.C. § 112, ¶ 2. Withdrawal of this rejection is therefore respectfully requested.

As an additional matter, Applicants note that claim 33 does not include the subject term “a TKPPR analogue” and thus should not have been included with this ground for rejection. To the extent the instant rejection is not removed, at least a correction of the instant status for claim 33 is respectfully requested.

II. Claims 1, 23-36 and 49 Satisfy 35 U.S.C. § 112, ¶ 1

Claims 1, 23-36 and 49 have been rejected under 35 U.S.C. § 112, ¶ 1, because the specification purportedly fails to “reasonably provide enablement for any analogue of TKPPR as monomer A, in the invention’s composition or method of ultrasound imaging. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make or use the invention commensurate in scope with these claims.” (*Final Office Action*, p. 3). Applicants respectfully traverse.

As an initial matter, the basis for this rejection is unclear. Specifically, as p. 3 of the *Final Office Action* admits, the Specification is enabling for practicing the claimed invention with A as a monomer of TKPPR. Therefore, it conclusively follows that the Specification is also enabling for practicing the claimed invention with A as a monomer of a TKPPR analogue since the chemistry of analogues are well understood by one of ordinary skill in the art. Moreover, as discussed, the recited limitation, “a monomer of a TKPPR analogue *that specifically binds to NP-1 cells or cells that express NP-1 with avidity that is equal to or greater than TKPPR*,” is narrower than that quoted by the Examiner and is fully enabled.

Furthermore, as discussed in **Section I**, *supra*, confirmation of this conclusion is supported by the thousands of U.S. Patents issued by the USPTO in the chemical, biological and drug classes which contain the term “analogues” or “analog” in the claims, thereby satisfying 35 U.S.C. § 112, ¶ 1.

In response to the arguments advanced on pp. 4-5 of the *Final Office Action*, Applicants note that the standard for determining whether the specification meets the enablement requirement is whether the experimentation needed to practice the invention is undue. MPEP 2164.01. Applicants submit that the answer is No. Specifically, one of ordinary skill in the art

would be able to practice the claimed invention without undue experimentation wherein A is a monomer of a TKPPR analogue that specifically binds to NP-1 cells or cells that express NP-1 with avidity that is equal to or greater than TKPPR. A review of the eight (8) *Wands* factors confirms this conclusion:

1. Breadth of the claims

Claims 1, 23-32, 34-36 and 49 are limited to compositions wherein, *inter alia*, A is a monomer of TKPPR or a monomer of a TKPPR analogue that specifically binds to NP-1 cells or cells that express NP-1 with avidity that is equal to or greater than TKPPR. Applicants note that this is a much narrower limitation than simply “a TKPPR analogue.”

Applicants further note that breadth of a claim should not be equated with indefiniteness. MPEP 2173.04. As such, the statement “With the substantial variability among what such an “analogue” could structurally be defined as; it is *not clear as to what may be included in the invention as claimed*” on p. 5 of the Office Action (emphasis added) is not applicable for an enablement analysis. As explained in **Section I**, *supra*, Applicants’ claims are definite and clear.

2. Nature Of The Invention

Claims 1, 23-32, 34-36 and 49 are directed to compositions of the formula A-L-B wherein, *inter alia*, A is a monomer of TKPPR or a monomer of a TKPPR analogue that specifically binds to NP-1 cells or cells that express NP-1 with avidity that is equal to or greater than TKPPR.

3. The State Of The Prior Art

In the drug, chemical, and biological field, it is well known and understood that a reference enabling the use of a parent compound would enable one of ordinary skill in the art to practice the claimed invention with an analogue of the parent compound. The USPTO has confirmed this conclusion by issuing thousands of patents in the drug, chemical and biological classes with the term “analogue” or “analog” in the claims.

4. The Level Of One Of Ordinary Skill

A person skilled in the art would be a scientist with an undergraduate degree in chemistry or biochemistry and at least two years of post graduate research experience in the field of diagnostic and therapeutic agents.

5. The Level Of Predictability In The Art

As the chemistry of analogues or analogs are well understood, there exists a level of predictability in the art between parent compounds and their analogues.

6. The Amount Of Direction Provided

The present Specification, as the *Final Office Action* admits on p. 3, is enabling for the claimed invention wherein A is a monomer of TKPPR.

The Specification further teaches TKPPR analogues that are useful in the present invention have specific characteristics – for example, they include molecules that target the NP-1 VEGF binding receptor with avidity that is greater than or equal to TKPPR (Specification, pages 10-11). Examples of acceptable TKPPR analogues are listed throughout the Specification, *e.g.*, at page 11, lines 25-30. The Specification lists examples of TKPPR analogues that result from,

e.g., amino acid substitutions, “made with synonymous groups” (page 11, lines 10-15); deletions or insertions of amino acids and muteins or peptides or polypeptides (page 11, lines 24); and peptidomimetics or pseudopeptides incorporating changes to the amide bonds of the peptide backbone (page. 11, lines 25-27).

7. The Existence Of Working Examples

No examples need to be provided in order to establish that the invention is adequately described. *See* MPEP § 2164.02 (“Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed”). This is especially true where the present Specification discloses the invention in such a manner that one skilled in the art will be able to practice the claimed invention with A as a TKPPR monomer without any undue experimentation. Nevertheless, the Specification does provide specific working examples with TKPPR analogues, *e.g.*, GTKPPR (Examples 4, 14, etc.). Thus, not only does the Specification provide working examples, but the statement “Applicant has not clearly described a single one of these ‘analogues’” on p. 5 of the *Final Office Action* is also incorrect.

8. The Quantity Of Experimentation Needed

The quantity of experimentation needed, if any, would not be undue. First, the claim limitation at issue is a narrow limitation, and not one directed to all TKPPR analogues as the *Final Office Action* asserts. (Factors 1-2, *supra*). Second, one of ordinary skill in the art with the prerequisite education and work experience would understand the chemistry of analogues, for which the state of

technology is well known in the art. (Factors 3-5, *supra*). Third, the present Specification both discloses and provides working examples of using TKPPR analogues. (Factors 6-7, *supra*). Therefore, for all of these reasons, one of ordinary skill in the art would be able to practice the claimed invention without undue experimentation.

As such, Applicants respectfully submit that the Specification is enabled for the pending claims and request that the rejection of claims 1, 23-36 and 49 under 35 U.S.C. § 112, ¶ 1 be reconsidered and withdrawn.

Additionally, as noted in **Section I**, *supra*, the term “a TKPPR analogue” is not present in claim 33. Thus, for this additional reason, withdrawal or correction of this rejection for at least claim 33 is respectfully requested.

III. Claims 1, 23-36 and 49 Are Patentable Over Pollak In View Of Barbera-Guillem

The *Final Office Action* maintained the rejection of claims 1, 23-36 and 49 under 35 U.S.C. § 103(a) as purportedly being unpatentable over Pollak in view of Barbera-Guillem. Applicants respectfully traverse.

In order to establish a *prima facie* case of obviousness, three factors must be shown: (1) there must be some suggestion or motivation to modify the reference or combine reference teachings; (2) there must be a reasonable expectation of success in the combination; and (3) the prior art reference or references must teach or suggest all of the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991); MPEP §§ 2142 and 2143. Applicants respectfully submit that a *prima facie* case of obviousness cannot be established since none of these three factors have been met.

1. There Is No Proper Motivation Or Suggestion To Combine

a. There Is No Motivation Or Suggestion To Combine The References

Pollak is directed to compositions and processes useful for generating metal-ligand complexes or metal-labelled compounds useful as imaging agents. (Pollak, col. 1, lines 3-6). On the other hand, Barbera-Guillem is directed to an optic system or fluorescence filter cube to detect fluorescence images of fluorescently labeled substrates. (Barbera-Guillem, col. 1, lines 7-11). There is no suggestion or motivation in the art to combine a reference directed to a metal imaging agent with a reference directed to a fluorescence filter cube.

The absence of any suggestion or motivation to combine is confirmed by the USPTO's placement of the asserted references in distinctly different classes. Pollak is classified in Classes 534 and 424, both directed to drugs, bio-affecting and body treating compositions. On the other hand, Barbera-Guillem has been classified in 356 (Optics), 250 (Radiant energy) and 359 (Optical systems and elements).

b. There Is No Motivation Or Suggestion To Make The Claimed Invention

Furthermore, for the sake of argument, even if combining the asserted references were permissible (Applicants maintain they are not), there is also no motivation or suggestion to combine the teachings of Pollak and Barbera-Guillem in the manner asserted by the *Final Office Action* to arrive at the presently claimed invention.

The *Final Office Action* states that that while Pollak does not expressly teach phospholipids as substrates, Barbera-Guillem teaches the use of phospholipids as substrates, and that therefore, the combination of the two references renders the present claims obvious (*Final Office Action*, page 6). However, this assertion is incorrect because both references use the term "substrate" to mean very different things when properly interpreting those terms in context of the

separate inventions disclosed in Pollak and Barbera-Guillem. As such, the asserted combination could only have been arrived at with the use of impermissible hindsight from Applicants' specification and claims. *Grain Processing Corp. v. American Maize-Products Co.*, 840 F.2d 902, 907, 5 USPQ2d 1788, 1792 (Fed. Cir. 1988) ("Care must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit."); *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."); MPEP 2142.

Pollak teaches compounds useful for generating an imaging agent that comprise: (1) a solid support (a "substrate"); (2) a linking group bound to the solid support; and (3) a ligand incorporating a metal coordinating atom that is coupled to a linking group by a bond that is cleaved in the presence of the metal (Pollak, column 2, lines 60-63; column 3, lines 2-10; claims 1, 13). Once the metal labeled ligand is released from the solid support substrate, the metal labeled ligand is collected for use as the imaging agent. (*Id.*, e.g., col. 2, lines 3-56; col. 6, lines 5-18, claim 11). Therefore, the solid support ("substrate") taught by Pollak is in actuality a platform for promoting the labeling reaction (*i.e.*, the complexing of the metal atom with the ligand to form a metal-ligand complex which serves as the imaging agent). (*Id.*, e.g., at col. 2, lines 47-56; col. 6, lines 5-18, claim 11). Furthermore, Pollak teaches that the acceptable "substrates" must have the capability of providing adequate support onto which the linking group can immobilize a ligand, and to which the linking group can remain bound "in its entirety under complex-forming reaction conditions" (Pollak, col. 4, lines 54-60). Pollak also states that this "substrate" is the solid support to which "the ligand of the conjugate is coupled covalently" and

which can also subsequently release only the labeled conjugate (*Id.* at col. 6, lines 8-18), thereby achieving the object of Pollak, which is the generation of a metal-ligand complex.

On the other hand, Barbera-Guillem teaches a fluorescence cube for providing fluorescence images of fluorescently labeled substrates (Barbera-Guillem, column 1, lines 7-9). The “substrate” is the *target* of the detection system to which the patented fluorescence cube is directed:

By the term “substrate” is meant, for the purposes of the specification to refer to a molecule of an organic nature (e.g., microorganism (bacterial, viral, etc.), tissue component, etc.) or inorganic nature (e.g., chemical), the presence and/or quantity of which is being tested for; and which contains a molecular component (domain or sequence or receptor or epitope or portion or chemical group or determinant) for which the affinity ligand has binding specificity (emphasis added)

(Barbera-Guillem, col. 5, lines 6-13). Barbera-Guillem lists phospholipids among the groups of targets (*i.e.*, “substrates”) that may be detected using fluorescence analysis (*Id.* at col. 5, line 19). Thus, it is clear that, as used therein, a “substrate” is the targeted molecule in the patient’s body for which the affinity ligand has binding specificity, thus furthering Barbera-Guillem’s object of detecting images of healthy or diseased tissue in patients using fluorescence imaging.

Thus, there is simply no motivation or suggestion to combine the teachings of Pollak and Barbera-Guillem in the manner asserted by the *Final Office Action* to arrive at the present invention, because both are referring to different “substrates” (*i.e.*, Pollak as a solid support for labelling reactions; Barbera-Guillem as a targeted molecule for fluorescence detection).

c. The Proposed Modification Would Impermissibly
Render The Asserted Art Unsatisfactory For Its Intended Purpose

As explained above, one of the key aspects of Pollak’s invention is the use of a solid support as a platform onto which the linking group can immobilize a ligand, and to which the linking group can remain bound “in its entirety under complex-forming reaction conditions”

before the conjugate ligand is cleaved from the support. (Pollak, col. 4, lines 54-60; col. 6, lines 8-18). As such the solid support substrate used by Pollak includes solid supports such as inorganic silica glass, silica or alumina beads, organic polystyrene, polyacrylamide or sugar polymers (Pollak, col. 4, lines 34-50). However, the use of phospholipids as proposed by the *Final Office Action* would impermissibly render Pollak's invention unsatisfactory for its intended purpose since a phospholipid would not be able to serve as a platform onto which the linking group can immobilize a ligand, and to which the linking group can remain bound "in its entirety under complex-forming reaction conditions" before the conjugate ligand cleaved from the support by the metal. (Pollak, col. 4, lines 54-60; col. 6, lines 8-18).

d. The Proposed Modification Impermissibly
Changes The Principle Of Operation Of The Asserted Reference

Not only would the use of phospholipids as solid supports impermissibly render Pollak's invention unsatisfactory for its intended purpose, but it would also impermissibly change the principle of operation for Pollak's invention, because there would be no suitable platforms onto which the linking group can immobilize a ligand, and to which the linking group can remain bound "in its entirety under complex-forming reaction conditions" before the conjugate ligand is cleaved from the support by the metal. (Pollak, col. 4, lines 54-60; col. 6, lines 8-18). Thus, for the same reason as discussed in the preceding paragraph, the asserted combination is improper.

As such, there is no motivation or suggestion to combine Pollack with Barbera-Guillem, and withdrawal of this rejection is respectfully requested.

2. There Is No Reasonable Expectation Of Success

There is further no reasonable expectation of success in combining the teachings of the Pollak and Barbera-Guillem. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438, 1442 (Fed.Cir.

1991). Both the motivation to combine and the reasonable expectation of success both must be found in the prior art and not Applicants' disclosure. *Id.* 20 U.S.P.Q.2d at 1442.

As explained in the preceding section, there is no reasonable expectation of success, based on the teachings of Pollak and Barbera-Guillem, that the use of phospholipids would serve as a viable platform in Pollak's invention onto which the linking group can immobilize a ligand, and to which the linking group can remain bound "in its entirety under complex-forming reaction conditions" before the conjugate ligand is cleaved from the support by the metal. (Pollak, col. 4, lines 54-60; col. 6, lines 8-18). No evidence has been provided to the contrary.

Therefore, for this additional reason, Applicants respectfully submit that it is improper to combine the Pollak and Barbera-Guillem references, and withdrawal of this rejection is respectfully requested.

3. The Asserted Reference Combination Fails To Teach All Limitations

In addition to lacking a motivation to combine and a reasonable expectation of success, the references, even if combined, still fail to teach all of Applicants' claimed limitations.

Independent claims 1, 23 and 49 each recite a compound with the formula A-L-B (*e.g.*, a linker (L) connecting the TKPPR monomer (A) to the phospholipid (B)).

Contrary to pp. 3-4 in the *Final Office Action*, the closest Pollak compound would be configured as follows: Solid Support - Linking Group - Ligand - TKPPR. (Pollak, *e.g.*, col. 2, lines 64-65, col. 3, line 64 to col. 4, line 9). Substituting Barbera-Guillem's phospholipid for the Solid Support element in Pollak would yield the following configuration: Phospholipid - Linking Group - Ligand - TKPPR. As such, the proposed combination would still fail to teach or suggest all of the claim limitations, and withdrawal of this rejection is respectfully requested.

Applicants note that the specific compounds recited in claim 33 are also not taught or suggested in any combination of Pollak and Barbera-Guillem. Therefore, in the event that the 35 U.S.C. § 103 rejection is not withdrawn in its entirety, the rejection of claim 33 should at least be withdrawn for this additional basis.

CONCLUSION

In view of the preceding amendments and remarks, Applicants maintain that the claims are now in condition for allowance, early notice of which is earnestly sought.

No fee(s) are believed to be due in connection with the filing of this *Amendment and Response*.

The Director is hereby authorized to charge any fees due or credit any overpayment to Deposit Account No. 50-0540.

If there are any outstanding issues the Examiner is respectfully invited to contact Applicants' undersigned attorneys to resolve them.

Respectfully submitted,

Dated: December 21, 2004

Rachel J. Lin Reg. No. 51,098

Donald L. Rhoads, Reg. No. 34,705
Rachel J. Lin, Reg. No. 51,098
KRAMER LEVIN NAFTALIS & FRANKEL LLP
919 Third Avenue
New York, New York 10022
(212) 715-9100 (telephone)
(212) 715-8000 (facsimile)